APGHN Archives of Pediatric Gastroenterology, Hepatology, and Nutrition

Case Report

Infantile Hyperchylomicronemia Due to A Novel GPIHBP1 Disease-Causing Variant Presenting with Milky Blood: A Rare Case Report

Iman Marzouq[1], Basant Elbanna[1], Sabine Schröder[2], Kornelia Tripolszki[2], Aida M. Bertoli-Avella[2], Aml Mahfouz[1]

[1] Paediatric Department, Faculty of Medicine, Alexandria University, Alexandria, Egypt

[2] CENTOGENE GmbH, Rostock, Germany

Corresponding author:
Basant Elbanna
b_abdelazim14@alexmed.edu.eg

Published:
31st May 2023

DOI:
https://doi.org/10.58427/apghn.2.2.2023.25-31

Citation:
Marzouq I, Elbanna B, Schröder S, Tripolszki K, Bertoli-Avella AM. Mahfouz A. Infantile Hyperchylomicronemia Due to A Novel GPIHBP1 Disease-Causing Variant Presenting with Milky Blood: A Rare Case Report. *Arch Pediatr Gastr Hepatol Nutr*. 2023;2(2):25-31.

Abstract:

Background: Familial hyperchylomicronemia is a very rare autosomal recessive disorder and the most severe type of pediatric hyperlipidemia. The purpose of this case report is to enhance clinician's insight on the diagnosis and management plan in the case of infantile hyperchylomicronemia presenting with milky blood.

Case: We reported a 2-month-old infant with familial chylomicronemia syndrome. The patient was 'accidentally' diagnosed by the observation of milky blood. Exome sequencing revealed a homozygous likely pathogenic GPIHBP1 variant (NM_178172.5:c.193T>C p.(Cys65Arg)) confirming the diagnosis. He was treated with low-fat diet, a formula rich in medium-chain triglycerides and fenofibrates. After 4 days, his serum triglycerides decreased markedly. Fenofibrates were stopped at the age of one year and his serum triglycerides were maintained at low level with dietary measures. No complications occurred during two years follow-up period.

Discussion: Clinical manifestations of familial chylomicronemia syndrome start in early life with a very high level of hypertriglyceridemia and with monogenetic etiology, in contrast to multifactorial chylomicronemia syndrome that starts in adulthood, with proposed polygenic etiology. The main treatment of familial chylomicronemia syndrome is dietary fat restriction to less than 15% of the total caloric intake and medium-chain triglycerides which can bypass the chylomicron pathway of fat metabolism.

Conclusion: The main challenge in this case was the early diagnosis to protect the patient against serious complications. The mainstay of therapy is low-fat diet and medium-chain triglycerides. This case illustrates the relevance of establishing a timely genetic diagnosis and treatment.

Keywords: chylomicronemia, GPIHBP1, milky blood, medium-chain triglycerides, fenofibrates

Introduction

Familial hyperchylomicronemia is a very rare autosomal recessive disorder.[1] Chylomicrons transport dietary fat in the circulation and very-low density lipoproteins (VLDL) transport endogenous triglycerides. Triglycerides are cleared from the circulation by lipoprotein lipase (LPL). Normally chylomicrons are cleared from the circulation by three to four hours after a meal.[2] The chylomicronemia syndrome (CS) may be due to monogenic (familial chylomicronemia syndrome (FCS)) or polygenic etiology.[1, 2] FCS is due to mutation in the LPL gene or cofactors responsible for regulation of its activity.[1] Clinical presentation includes milky blood, hepatomegaly, xanthoma, lipemia retinalis, and acute pancreatitis.[1] The main treatment of FCS is dietary fat restriction to less than 15% of the total caloric intake and medium chain triglycerides.[1, 2]

Case

A two-month-old infant born to a first cousin marriage was exclusively breastfed since birth. He had two older healthy siblings. He presented to us at the emergency ward with parental concern of irritability. Physical examination revealed low-grade fever, unexplained irritability, anthropometric measures were average to age, lax abdomen, no organomegaly nor xanthomas, and fundus examination was negative for lipemia retinalis. Milky blood was reported during blood sampling (**Figure 1**). Subsequent laboratory investigations are shown in **Table 1**. The results of lipid electrophoresis are shown in **Table 2**.

Figure 1. Milky blood presenting in the case

Given the very high level of serum triglycerides, fasting hyperchylomicronemia and after exclusion of secondary causes (normal liver, renal function, thyroid profile, and random blood sugar), the possible diagnosis of FCS was suggested. He was admitted on intravenous fluids and formula rich in medium-chain triglycerides (MCT), he received fenofibrates 40 mg orally and omega-3 fatty acids. His symptoms improved after two days. His serum triglycerides markedly decreased (1197 mg/dL) after 4 days and he was discharged. Upon introduction of breastfeeding (25%) concomitantly with MCT formula (75%) for 1 week, serum triglyceride level increased again (3906

mg/dL). Thus, breastfeeding was stopped and continued with MCT formula, fibrates and omega-3 fatty acids. Lipid profile for all tested family members was normal. On follow-up visits, he was maintained on low-fat diet and same management. He acquired normal developmental milestones. At one year of age, fenofibrate therapy was stopped and the therapy was continued low-fat diet, MCT formula, and omega-3 fatty acids. His follow-up serum triglyceride level did not exceed 1000 mg/dL for two years period and without any complications.

Table 1. Initial laboratory investigations

Parameters	Result	Reference range[3, 4]
White blood cells	15.64	(5.5-17) 10^3/ uL
Hemoglobin	9.5!	(10.6-13.7) g/ dL
Platelet count	646	(150-500) 10^3/ uL
ALT	12	Up to 45 U/L
Urea	11	(10-50) mg/dL
BUN	5	(6-23) mg/dL
Creatinine	0.22	(0.2-0.4) mg/dL
Total cholesterol	119	Up to 200 mg/dL
Triglycerides	20364*	Up to 200 mg/dL
HDL-Cholesterol	8	More than 35 mg/dL
LDL-Cholesterol	48	Up to 140 mg/dL
TSH	4.8	(1.7-9.1) uIU/ml
Free T4	1.2	(0.8-2) ng/dL

*very high triglycerides level, !normocytic normochromic anemia

Table 2. Results of lipid electrophoresis

Parameters	Result	Reference range[3, 4]
Alpha Lipoprotein	1 %	22-46 %
Pre Beta Lipoprotein	49%	Up to 27%
Beta Lipoprotein	3%	47-71%
Chylomicrons	47%	Absent

To identify the cause of chylomicronemia, DNA was extracted from dried blood spot (DBS) on filter card (CentoCard ®). Exome sequencing was performed as previously described, using the Twist Human Core Exome Plus Kit and sequencing on an Illumina platform to obtain at least 20x coverage depth for >98% of the targeted bases.[5] An inhouse (CENTOGENE) bioinformatics pipeline, including read alignment to GRCh37/hg19 genome assembly, variant calling, annotation, and comprehensive variant filtering was applied. The analysis revealed a homozygous missense variant in the GPIHBP1 gene: NM_178172.5:c.193T>C, p.(Cys65Arg). This result confirmed the clinical diagnosis of monogenic FCS. The detected variant is extremely rare (not present in any public database), and the in-silico tools predict that this variant is damaging. In CENTOGENE's bio-databank, this GPIHBP1 variant

has been detected in two additional patients from Egypt, presenting with a similar phenotype. The variant is classified as likely pathogenic according to the ACMG-ClinGen established criteria.

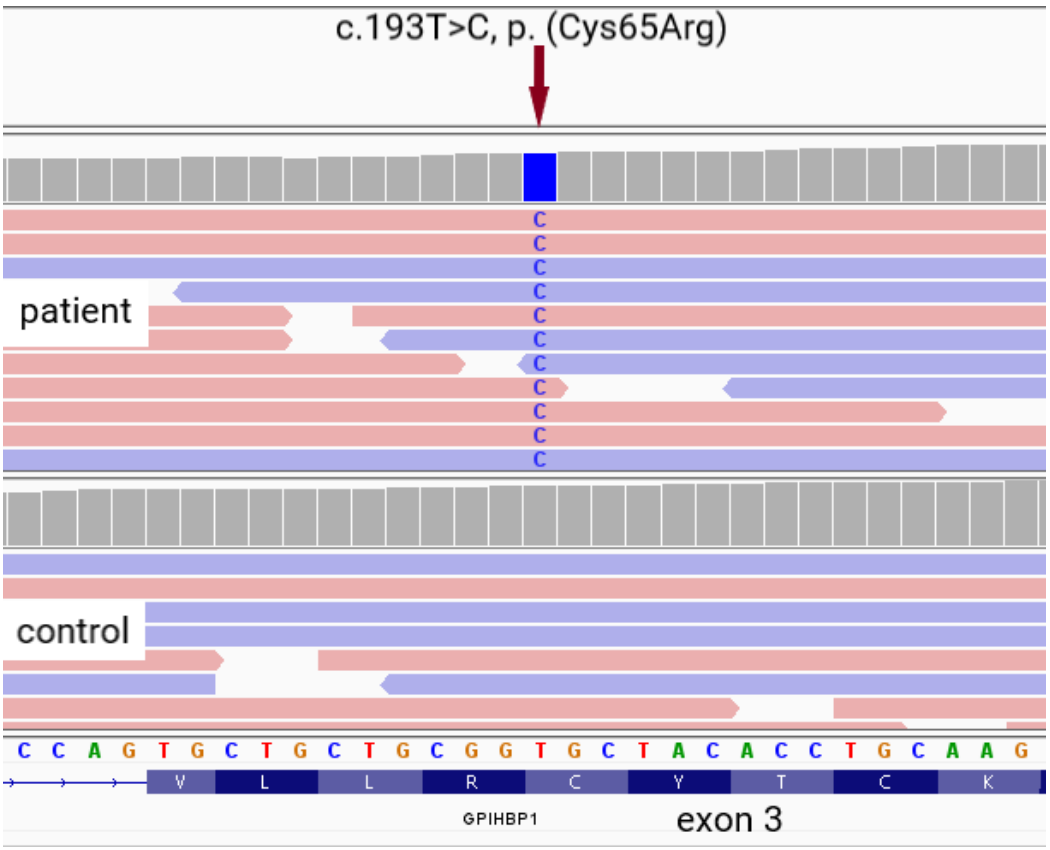

Figure 2. Bam file showing the GPIHBP1 (NM_178172.5:c.193T>C p.(Cys65Arg)) variant indicated with arrow. Total read count with the variant is 113 (variant allele frequency: 100%). Visualized by the Broad Institute Integrative Genomics Viewer.

Discussion

We present the case of an Egyptian patient with an early clinical and genetic diagnosis of familial Chylomicronemia Syndrome (FCS). Timely medical treatment was implemented with favorable response and absence of clinical complications.

Clinical manifestations of FCS start in early life with a very high level of hypertriglyceridemia and with monogenetic etiology, in contrast to multifactorial chylomicronemia syndrome that starts in adulthood, with proposed polygenic etiology.[2] The studied case had very high hypertriglyceridemia (> 20000 mg/dL), with fasting chylomicronemia in early infancy. A genetic diagnosis was established by exome sequencing and the detection of a rare homozygous likely pathogenic variant in GPIHBP1, c.193T>C p.(Cys65Arg). Previous case studies reported missense and loss of function variants (nonsense, deletions, duplications, splicing) in the same gene, with 51 variants registered in Human Gene Mutation Database (HGMD). Several authors have reported missense variants affecting the same Cys65 residue detected in our case. Olivecrona et al.[6] reported three siblings with mutations involving cysteines in the Ly6 domain of GPIHBP1 (Cys65Ser and Cys68Gly). Also, Franssen et al.[7] reported a young boy with the variant Cys65Tyr, suggesting that these residues are relevant for the protein function.

FCS can present with nonspecific symptoms such as fever and irritability.[8] Milky blood can be detected during blood sampling, as reported in the current case.[1] Similar findings were reported by Mo Kyung Jung et al.[8], Nehal M. El-koofy et al.[9], N. El Idrissi Slitine et al[10], and Shwetha Kuthiroly et al.[11]. Other clinical presentations include eruptive xanthoma, lipemia retinalis and hepatomegaly.[11, 12, 13, 14] The most serious complication in FCS is the development of acute pancreatitis.[11,14] Other clinical complications include chylothorax, cerebral thrombophlebitis, lipid encephalopathy.[11, 13, 15, 16] The studied case presented only with irritability and milky blood with no hepatomegaly, xanthoma, lipemia retinalis nor pancreatitis. The prevention of these complications is likely due to the early diagnosis and treatment.

The main treatment of FCS is dietary fat restriction to less than 15% of the total caloric intake and medium-chain triglycerides which can bypass the chylomicron pathway of fat metabolism.[1, 2] High doses of omega-3 fatty acids (4–6 gram eicosapentaenoic acid (EPA) or doxosahexaenoic acid (DHA) daily) can reduce the production of VLDL and size of chylomicrons. It can also activate LPL lipolysis by apo C3 inhibition.[1] Lipid-lowering drugs as fibrates, nicotinic acid and statins are not Food and Drug Administration (FDA) approved for use in pediatrics younger than 18 years of age. Their use in marked hypertriglyceridemia is of little effect.[1] Lipid apheresis can be used in severe hypertriglyceridemia.[1] The studied case was treated with low-fat diet, medium-chain triglycerides, fibrates, and omega-3 fatty acids. Although it is

recommended not to stop breastfeeding[17], our attempts to breastfeeding were unsuccessful as reported previously by Callum J et al.[13] and Nehal M. El-koofy et al.[9]

Conclusion

We present a young patient clinically diagnosed with FCS, and genetically confirmed by exome sequencing with a novel likely pathogenic variant in GPIHBP1. We highlight the importance of early disease detection and treatment to prevent severe complications such as cerebral complications and acute pancreatitis. Screening of hyperchylomicronemia could be considered as part of the newborn screening program.

Conflict of Interest

Sabine Schröder, Kornelia Tripolszki, Aida M. Bertoli-Avella are employees of CENTOGENE GmbH.

Funding Statement

The authors confirm that the presented case study did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

Acknowledgement

The authors would like to thank the Alexandria University Children's Hospital nursing staff for providing the needed care.

References

1. Brahm AJ, Hegele RA. Chylomicronaemia--current diagnosis and future therapies. Nat Rev Endocrinol. 2015;11(6):352-62.https://doi.org/10.1038/nrendo.2015.26
2. Goldberg RB, Chait A. A Comprehensive Update on the Chylomicronemia Syndrome. Front Endocrinol (Lausanne). 2020;11:593931.https://doi.org/10.3389/fendo.2020.593931
3. Bain BJ, Bates I, Laffan MA. Dacie and lewis practical haematology e-book: Elsevier Health Sciences; 2016.
4. Rifai N. Tietz textbook of clinical chemistry and molecular diagnostics-e-book: Elsevier Health Sciences; 2017.
5. Trujillano D, Oprea GE, Schmitz Y, Bertoli-Avella AM, Abou Jamra R, Rolfs A. A comprehensive global genotype-phenotype database for rare diseases. Mol Genet Genomic Med. 2017;5(1):66-75.https://doi.org/10.1002/mgg3.262
6. Olivecrona G, Ehrenborg E, Semb H, Makoveichuk E, Lindberg A, Hayden MR, et al. Mutation of conserved cysteines in the Ly6 domain of GPIHBP1 in familial chylomicronemia. J Lipid Res. 2010;51(6):1535-45.https://doi.org/10.1194/jlr.M002717
7. Franssen R, Young SG, Peelman F, Hertecant J, Sierts JA, Schimmel AW, et al. Chylomicronemia with low postheparin lipoprotein lipase levels in the setting of GPIHBP1 defects. Circ Cardiovasc Genet. 2010;3(2):169-78.https://doi.org/10.1161/circgenetics.109.908905
8. Jung MK, Jin J, Kim HO, Kwon A, Chae HW, Kang SJ, et al. A 1-month-old infant with chylomicronemia due to GPIHBP1 gene mutation treated by plasmapheresis. Ann Pediatr Endocrinol Metab. 2017;22(1):68-71.https://doi.org/10.6065/apem.2017.22.1.68
9. El-koofy NM, Abdo YA, El-Fayoumi D, Esmael AF, Elmonem MA, Ezzeldin Z. Management strategy and novel ophthalmological findings in neonatal severe hypertriglyceridemia: a case report and literature review. Lipids in Health and Disease.

2021;20(1):38.https://doi.org/10.1186/s12944-021-01464-2
10. El Idrissi Slitine N, Bennaoui F, Louachama O, Habibi L, Fdil N, Tali A, et al. Lipoprotein Lipase (LPL) Gene Mutation: A First Report in Children. International Journal of Pediatrics. 2017;5(10):5839-42.https://doi.org/10.22038/ijp.2017.25461.2163
11. Kuthiroly S, Yesodharan D, Radhakrishnan N, Ganapathy A, Mannan AU, Hoffmann MM, et al. Lipoprotein Lipase Deficiency. Indian J Pediatr. 2021;88(2):147-53.https://doi.org/10.1007/s12098-020-03305-z
12. Sustar U, Groselj U, Khan SA, Shafi S, Khan I, Kovac J, et al. A homozygous variant in the GPIHBP1 gene in a child with severe hypertriglyceridemia and a systematic literature review. Frontiers in Genetics. 2022;13.https://doi.org/10.3389/fgene.2022.983283
13. Wilson CJ, Priore Oliva C, Maggi F, Catapano AL, Calandra S. Apolipoprotein C-II deficiency presenting as a lipid encephalopathy in infancy. Ann Neurol. 2003;53(6):807-10.https://doi.org/10.1002/ana.10598
14. Aycan Z, Berberoğlu M, Ocal G, Altundas N, Adiyaman P, Evliyaoğlu O. Neonatal diabetes with hyperchylomicronemia. Indian J Pediatr. 2002;69(12):1087-9.https://doi.org/10.1007/bf02724395
15. Onci Es S, Lamzouri O, Bouchlarhem A, Haddar L, Mohammed A, mimouni H, et al. A very rare case of chylomicronemia revealed by cerebral thrombophlebitis in a 4-month-old infant. Ann Med Surg (Lond). 2022;75:103276.https://doi.org/10.1016/j.amsu.2022.103276
16. Millichap J. Apolipoprotein C-II Deficiency with Encephalopathy. Pediatric Neurology Briefs. 2003;17(7). https://doi.org/10.15844/pedneurbriefs-17-7-8
17. Rohrs HJ, Berger S. Pediatric lipid disorders in clinical practice. Medscape [Internet] Accessed. 2016;10